Paper No. 41

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte MERTON BERNFIELD, and OFER REIZES

Appeal No. 2003-1676
Application No. 08/965,356

ON BRIEF

Before WINTERS, MILLS and GREEN, Administrative Patent Judges.

GREEN, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 112 first paragraph from the examiner's final rejection of claims 1, 3-5, 10 and 12-14. Claims 1 and 10 are representative of the subject matter of the appeal and read as follows:

1. A transgenic rodent whose genome comprises a stably integrated DNA sequence encoding a syndecan operably linked to a promoter, wherein expression of the DNA sequence results in the rodent developing maturity onset obesity.

10. A method for screening for compounds which can alter body weight comprising: administering a compound to a transgenic rodent whose genome comprises a stably integrated DNA sequence encoding a syndecan operably linked to a promoter, wherein expression of the DNA sequences results in the

rodent developing maturity onset obesity, and expression of the DNA sequences results in the rodent developing maturity onset obesity, and observing whether there is a change in body weight over a period of time.

The examiner relies upon the following references:

Hammer et al. (Hammer), "Spontaneous inflammatory disease in transgenic rats expressing HLA-B27 and human β_2m: an animal model of HLA-B27-associated human disorders" Cell, Vol. 63, pp. 1099-1112 (1990).

Mullins et al. (Mullins 1989), Expression of the DBA/2J Ren-2 gene in the adrenal gland of transgenic mice" EMBO Journal, Vol. 8, pp. 4065-4072 (1989).

Mullins et al. (Mullins 1990), "Fulminant hypertension in transgenic rats harbouring the mouse Ren-2 gene" Nature, Vol. 344, pp. 541-544 (1990).

Taurog et al. (Taurog), "HLA-B27 IN INBRED AND NON_INBRED TRANSGENIC MICE: Cell surface expression and recognition as an alloantigen in the absence of Human β_2-microglobin" Journal of Immunology, Vol. 141, pp. 4020-4023 (1988).

Wall, "Transgenic livestock: progress and prospects for the future," Theriogenology, Vol. 45, pp. 57-68 (1996).

Appellants rely upon the following references:

Wang et al. (Wang), "Central delivery of human tissue kallikrein gene reduces blood pressure in hypertensive rats," BBRC, Vol. 244, pp. 449-454 (1998).

Ideda et al. (Ideda), "Obesity and insulin resistance in human growth hormone transgenic rats," Endocrinology, Vol. 139, pp. 3057-3063 (1998).

Bartke et al. (Bartke), "Effects of growth hormone overexpression and growth hormone resistance on neuroendorcrine and reproductive functions in transgenic and knock-out mice," Proc. Soc. Exp. Biol. Med., Vol. 222, pp. 113-123 (1999).

Charreau et al. (Charreau), "Transgenesis in rats: technical aspects and models," Transgenic Res., Vol. 4, pp. 223-234 (1996) (Abstract Only).

Flier et al. (Flier), "Obesity and the hypothalamus: novel peptides for new pathways," Cell, Vol. 92, pp. 437-440 (1998).

Augustine et al. (Augustine), "Rodent mutant models of obesity and their correlations to human obesity," The Anatomical Record, Vol. 257, pp. 64-72 (1999).

Frederich et al. (Frederich), "Leptin levels reflect body lipid content in mice: evidence for direct induced resistance to leptin levels," Natl. Med., Vol. 12, pp. 1311-1314 (1995).

Surwit et al. (Surwit), "Low plasma leptin in response to dietary fat in diabetes- and obesity-prone mice," Diabetes, Vol. 46, No. 9, pp. 1516-1520 (1997).

Suga, et al. (Suga), "Effects of fructose and glucose on plasma leptin, insulin, and insulin resistance in lean and VMH-lesioned obese rats," Am. J. Physiol. Endocriol. Metab., Vol. 5, pp. E677-83, (2000).

Wang, et al. (Wang 2000), "Leptin resistance of adipoctes in obesity: role of suppressors cytokine signaling," Biochem. Biophys. Res. Commun., Vol. 277, No., pp. 20-26 (2000).

Wang et al. (Wang 1999), "Comparing the hypothalamic and extrahypothalamic actions endogenous hyerleptinemia," Proc. Nat'l Acad. Sci., Vol. 96, No. 1, pp. 10373-10378, (1999).

Spiegelman et al. (Spiegelman), "Adipogenesis and obesity: rounding out the big picture," Cell, Vol. 87, pp. 377-389, (1996).

Claims 1, 3-5, 10, and 12-14 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, i.e., failure to provide an enabling disclosure. After careful review of the record and consideration of the issue before us, we affirm.

PROCEDURAL HISTORY

Claims 6 and 15 are also pending, but are free of rejection. These claims are limited to rodents having the genotype FVB/TgN(synd-1).

The claims were objected to in the Examiner's Answer because they were dependent claims that depended upon rejected independent claims. See Examiner's Answer, page 2. The examiner indicated that the claims would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. See id. The claims were amended as requested, but the examiner did not enter the proposed amendments. See Advisory Action, page 3, Paper No. 31. The examiner stated that the proposed amendment would include both a broad and narrow term requiring a new grounds of rejection under 35 U.S.C. § 112, second paragraph for indefiniteness. See id. The examiner claimed that the broad term "transgenic rodent" contradicted the later narrow term genotype FVB because the genotype limited the claim to mice. See id. The appellant petitioned for entry of amendment and the petition was granted.

The issue to be decided on appeal is whether the specification enables claims drawn to transgenic rodents. While claims 6 and 15 contain the broad claim language "rodent," the claims are self-restricted by the later FVB genotype language.[1] We interpret the FVB genotype to refer to mice only. Thus, claims 6 and 15 are limited to mice having the genotype FVB/TgN(synd-1), and are not subject to the rejection under 35 U.S.C. § 112, first paragraph.

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[1] The specification describes FVB mice on pages 12 and 25. Page 3 of the Advisory Action, Paper No. 31, explains that the term FVB refers to a specific mouse strain.

BACKGROUND

As noted by the specification, "[o]besity is a well established risk factor for a number of potentially life-threatening diseases." Id. at 1. "By contributing to greater than 300,000 deaths per year, obesity ranks second only to tobacco smoking as the most common cause of potentially preventable death." Id. A major reason for the long-term failure of established approaches for dealing with obesity is a poor understanding of the mechanisms of obesity. See id at 1-2.

While not all of the mechanisms involved in the regulation of weight gain are known, it is believed that many genetic and environmental factors play major and interrelated roles. See id. at 3. "Evidence accumulating over the past several years indicates that hormones, neuropeptides and neurotransmitters act on the hypothalamus to establish a 'set point' that maintains a balance between feeding behavior and energy expenditure. A very small change in this set point can cause severe obesity or its extreme, starvation." Id. at 7.

The specification teaches further that complex cellular behaviors, such as those involved in wound repair, may be influenced by a variety of soluble growth factors, cytokines, and insoluble extracellular matrix compounds. See id. Many of those molecules need bind to heparin sulfate chains at the surface of nearly all adherent cells in order to exert their effects. See id. Syndecan-1 is a major transmembrane heparin sulfate proteoglycan that is induced transiently on mesenchymal cells during the repair of skin wounds, and its expression is highly regulated in vivo. See id. at 8.

Expression of the syndecan-1 transgene in the hypothalamus appears to interfere with the natural set point mechanism that balances feeding and energy expenditure. See id. at 7. It is believed that the interference occurs through an interaction with the weight regulating melanocortin-4 receptor, which is known to be involved in weight regulation. See id.

The specification describes the creation of a syndecan-1 construct with specificity to the hypothalamus of the brain.[2] See id. at 10. The construct consists of two essential elements: (1) a promoter to localize hypothalamic expression, and (2) a nucleic acid molecule encoding a syndecan. See id. The specification teaches further that transgenic animals may be produced using the construct. See id. at 12. The specification, however, only exemplifies the production of a transgenic mouse. See id.

DISCUSSION

Appellants argue that the claims do not stand or fall together. Appellants, however, only point out the differences in what the claims cover. See Appeal Brief, page 3. Merely pointing out differences in what the claims cover is not an argument as to why the claims are separately patentable. See 37 C.F.R. 1.192(c)(7); In re Dance, 160 F.3d 1339, 1340 n.2, 48 USPQ2d 1635, 1636 n.2 (Fed. Cir. 1998) (noting that dependent claims not argued separately on the

[2] After an initial rejection based partially upon a lack of evidence showing syndecan expression in the hypothalamus, appellants presented a declaration accompanied by data showing specificity of the CMV promoter within the hypothalamus.

merits rise or fall with the independent claim to which they relate). Therefore, we focus our analysis on claim 1, the broadest claim.

The examiner bears the initial burden of showing nonenablement. See In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The specification must teach those skilled in the art to make and use the full scope of the claimed invention without undue experimentation. See Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1371, 52 USPQ2d 1129, 1135 (Fed. Cir. 1999). "That some experimentation may be required is not fatal; the issue is whether the amount of experimentation required is not 'undue.'" In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (citation omitted, emphasis in original). "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The factual considerations discussed in Wands are: (1) the quantity of experimentation necessary to practice the invention, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. We agree with the examiner that the specification has not enabled one skilled in the art to produce a rodent other than a mouse displaying the claimed phenotypic characteristic of obesity.

The first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims. As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. See In re Moore, 439 F.2d 1232, 1236, 169 USPQ 236, 239 (CCPA 1971). The claims are drawn to a "transgenic rodent." As the examiner points out, the scope of the claims is broad, as over 4000 species are encompassed by the term "rodent," and includes "squirrels, chipmunks porcupines, woodchucks, gophers, gerbils, chinchillas, etc." Examiner's Answer, page 13. Only one rodent, i.e., the mouse, was demonstrated in the specification to show phenotypic results. Id. at 6.

As to the nature of the invention, the claims are drawn to a transgenic rodent that comprises a stably integrated DNA sequence encoding a syndecan operably linked to a promoter, wherein the expression of the DNA sequence results in the rodent developing maturity onset obesity, i.e., the claims require phenotypic expression of the syndecan. As the examiner emphasizes, the nature of the invention is thus drawn to phenotypic expression of the syndecan gene in rodents, and not merely expression of the transgene in the rodents. See id. at 6.

With respect to the unpredictability and the state of the art, the examiner asserts that "[t]he specification fails to provide an enabling disclosure for the preparation of any species of transgenic rodent of the type claimed because the

phenotype of a transgenic animal cannot be predicted." Id. at 6. The examiner contends that "phenotypic alterations resulting from the introduction of a transgene into an animal's genome cannot be predicted, even when the function of the gene is known." Id. The examiner argues further that because phenotypic alterations resulting from transgene introduction cannot be predicted and in the absence of a transgene-dependent phenotype, one skilled in the art would not know how to use the claimed animals. See id. at 6.

The examiner contends that phenotypic expression cannot be predicted in different species because of a variety of factors including transgenic expression depending on the particular gene construct used and the integration site of the construct. See id. at pages 6-7. Moreover, according to the examiner, there are inherent physiological differences between species of rodents that can affect the phenotype in an unpredictable manner. See id. at 8.

The examiner supports the conclusion that art is unpredictable by pointing out that the transgene designs for results encompassing different animals are not clearly understood in the prior art, and that

> examples in the literature demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, several animal models of human diseases have relied on transgenic rats when development of mouse models was not feasible. Mullins [ ] 1990 produced outbred Sprauger-Dawley x WKY rats with hypertension caused by expression of a mouse Ren-2 renin transgene. Hammer [ ] 1990 describe spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human b_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human

> disease-like symptoms in transgenic mice (Mullins [ ] 1989; Taurog [ ] 1988) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats.

Id. at 8-9. The above studies thus demonstrate that phenotypic expression in different species is unpredictable in different species of rodents expressing the same transgene.

The examiner further cites Wall to further support the general difficulty in designing transgenes with predictable behaviors because of a lack of understanding on essential genetic control elements. See id. at 7. Walls points out that "transgene expression and the physiological consequences of transgene products in livestock are not always accurately predicted in transgenic mouse studies," and that the physiological consequences of transgene expression are not always predicted in transgetic mouse studies and the only approach yielding truly active data is testing transgenes in the livestock species of interest. Wall 1996, page 62.

Next, with respect to the amount of guidance provided by the specification, the examiner determined that while the specification confers the capability to perform a genetic transfer resulting in the expression of a transgene, a predictable phenotype cannot be achieved. See id. at 12-13. Because of this, the examiner argues that the specification has not enabled one skilled in the art to produce a rodent other than a mouse displaying the phenotypic characteristices claimed. See id. The examiner also contends that there is little

guidance presented for gaining phenotypic results in the other 3,999 species of rodents encompassed by the claims. See id. at 13.

Finally, the examiner determined that the specification needed a large quantity of experimentation to produce phenotypic rodents other than mice. See Examiner's Answer, page 5. The examiner also points out that some of the animals included in the rodent claims have not had syndecans identified. See id. at 9. The specification details transgenic expression in mice and claims it is the same for all animals, however, the examiner argues that some species have less advanced genetic studies. See id. at 8.

Analysis of the Wands factors compels us to affirm the rejection. The prior art shows an unpredictable field with little guidance for the 4,000 different species of rodents claimed, and therefore, the appellant has failed to enable the entire scope of the claimed invention.

Appellants assert that "[i]t is the opinion of the inventors, who are skilled in the field of obesity and transgenic rodents, that studies done to make and screen compounds using genetically engineered mice are predictable of the same results in rats." Appeal Brief, page 8 (emphasis in original). Appellants assert that the microinjection technique used to introduce the transgene can be used on a variety of animals and that the methods would be the same on both rats and mice. See id. at 9. Appellants supply post-filing date art references showing phenotypic expression of hGH transgene expression and phenotype in both rats and mice. See Ideda 1998 and Bartke 1999. Appellants, however, cannot rely

on post-filing art references to show what one skilled in the art would know at the time of filing. The state of the art at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. See In re Gunn, 537 F.2d 1123, 1128, 190 USPQ 402 (CCPA 1976).

Moreover, the remaining references relied upon by the appellants to counter the rejection are not drawn to transgenic experiments resulting in similar phenotypic results between animals within the rodent species. Instead, the references study knock-out mutations or surgical lesions leading to obesity in rats and mice only. See Wang 1998 (expression of kallikrein gene expressed in the hypothalic nuclei of rats after intracerebroventricular injection, however, rats are not transgenic rats and no phenotypic results discussed); Flier 1998 (surgical lesions in the hypothalamus cause onset obesity); Augustine 1999 (review of research on gene function in the hypothalamus showing knock-out mutants and transgene over-expression models have revealed possible genetic causes of obesity); Suga 2000, (obese rat leptin concentration study on different diets and effects on the leptin level where the rats studied were VMH-lesioned); and Wang 2000 (study of leptin in VMH-lesioned obese rats). In addition, an abstract attached to the reply brief submitted by the appellant actually refutes the position put forth by the appellant by showing differences in data gained in transgenic

studies with both rats and mice. As noted by the abstract, "[i]n some instances, the production of transgenic rats has provided data that are new and relevant, compared to data obtained in mice bearing the same transgene." See Charreau 1996.

Appellants also argue that the claims are limited to those animals expressing a stably integrated DNA encoding a syndecan, where the animal exhibits maturity onset obesity. See Appeal Brief, page 12. Appellants assert that "[e]ven if one skilled in the art had trouble making a rat with a specified phenotype . . ., it is clear that a rat not having the claimed phenotype would not be within the claim. The claims are limited to those animals expressing a stably integrated DNA encoding a syndecan, where the animal exhibits maturity onset obesity." Id. To accept appellants' argument, however, would virtually render moot the requirement under 35 U.S.C. § 112, first paragraph, that the specification need enable the full scope of the claimed invention. The examiner has set forth evidence and reasoning demonstrating that extrapolating expression of a desired phenotype, and not just gene expression, from a single example is unpredictable, and those skilled in the art would still be forced to experiment in the 3,999 other rodents to see if they displayed the claimed characteristic, and thus it would require an undue amount of experimentation to practice the full scope of the claimed subject matter.

Appellants argue further that the failure to have reduced to practice all embodiments that may fall within the scope of the claims is not proof of non-

enablement. See id. at 13. Appellants state that they are a small, non-profit institution unable to test all of the species. See id. Appellants also contend that the issue on appeal is analogous to that in In re Wands where the Federal Circuit found that the production of claimed monoclonal antibodies in only 2.3% of attempts to make such antibodies was an acceptable amount of experimentation.

Appellants' arguments are not deemed to be convincing. Appellants' claims encompass phenotypic expression of the syndecan gene in over 4,000 species of rodents, whereas the specification only sets forth a single working example. When this is combined with the unpredictable state of the prior art and undue experimentation needed, as described above, the specification fails to enable the skilled artisan to practice the full scope of the claimed invention.

In addition, the presently claimed subject matter is not analogous to the art involved in In re Wands, in which antibodies are screened for the desired binding activity, wherein it is assumed that a percentage of the pool produces the monoclonal antibody sought. See Examiner's Answer, page 16. With respect to the production of transgenic animals, there is no assumption that a certain percentage of the transgenic animals that express the transgene will have the desired phenotyoe. Id. at 16-17. That is, "in the monoclonal antibody situation, the probability of the desired hybridoma being present is 100%, even if only 2.3% of the hybridomas in the pool are the correct one; then it is just a matter of

identifying and isolating the correct one. In the case of transgenics, the 'correct' one, i.e. the one with the desired phenotype may not be present at all." Id. at 17.

Appellants assert that the burden of proof was shifted to the examiner who has presented no additional evidence in response to the appellant's evidence. See Appeal Brief, page 14. Appellants, however, base their arguments that the burden has shifted on unrelated and post-dated references (see above) while the references supplied by the examiner show unpredictability in the field at the time of application. Appellants have failed to supply any evidence showing a correlation between transgenic expression and phenotype in the 4,000 different species of rodents showing only expression in mice and supplying post-filing references on surgical lesions and loss of function mutations.

CONCLUSION

For the reasons stated above, the rejection of claims 1, 3-5, and 12-14 under 35 U.S.C. § 112, first paragraph, for lack of enablement is affirmed.

No time period for taking any subsequent action in connection with this Appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

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